Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis

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Abstract: BACKGROUND AND PURPOSE Recent observations linked coronavirus disease 2019 (COVID-19) to thromboembolic complications possibly mediated by increased blood coagulability and inflammatory endothelial impairment. We aimed to define the risk of acute stroke in patients with severe and non-severe COVID-19. METHODS We performed an observational, multicenter cohort study in four participating hospitals in Saxony, Germany to characterize consecutive patients with laboratory-confirmed COVID-19 who experienced acute stroke during hospitalization. Furthermore, we conducted a systematic review using PubMed/MEDLINE, Embase, Cochrane Library and bibliographies of identified papers following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines including data from observational studies of acute stroke in COVID-19 patients. Data were extracted by two independent reviewers and pooled with multicenter data to calculate risk ratios (RRs) and 95% confidence intervals (95% CIs) for acute stroke related to COVID-19 severity using a random-effects model. Between-study heterogeneity was assessed using Cochran's Q and I^2 statistics. International Prospective Register of Systematic Reviews registration number: CRD42020187194. RESULTS Of 165 patients hospitalized for COVID-19 (49.1% males, median age = 67 years [57-79 years], 72.1% severe or critical) included in the multicenter study, overall stroke rate was 4.2% (95% CI: 1.9-8.7). Systematic literature search identified two observational studies involving 576 patients that were eligible for meta-analysis. Amongst 741 pooled COVID-19 patients, overall stroke rate was 2.9% (95% CI: 1.9-4.5). Risk of acute stroke was increased for patients with severe compared to non-severe COVID-19 (RR = 4.18, 95% CI: 1.7-10.25; P = 0.002) with no evidence of heterogeneity (I^2 = 0%, P = 0.82). CONCLUSIONS Synthesized analysis of data from our multicenter study and previously published cohorts indicates that severity of COVID-19 is associated with an increased risk of acute stroke.

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ORIGINAL ARTICLE

Increased risk of acute stroke among patients with severe COVID-19: a multicenter study and meta-analysis

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Keywords:
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Background and purpose: Recent observations linked coronavirus disease 2019 (COVID-19) to thromboembolic complications possibly mediated by increased blood coagulability and inflammatory endothelial impairment. We aimed to define the risk of acute stroke in patients with severe and non-severe COVID-19.

Methods: We performed an observational, multicenter cohort study in four participating hospitals in Saxony, Germany to characterize consecutive patients with laboratory-confirmed COVID-19 who experienced acute stroke during hospitalization. Furthermore, we conducted a systematic review using PubMed/MEDLINE, Embase, Cochrane Library and bibliographies of identified papers following Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines including data from observational studies of acute stroke in COVID-19 patients. Data were extracted by two independent reviewers and pooled with multicenter data to calculate risk ratios (RRs) and 95% confidence intervals (95% CIs) for acute stroke related to COVID-19 severity using a random-effects model. Between-study heterogeneity was assessed using Cochran's Q and I^2 statistics. International Prospective Register of Systematic Reviews registration number: CRD42020187194.

Results: Of 165 patients hospitalized for COVID-19 (49.1% males, median age = 67 years [57–79 years], 72.1% severe or critical) included in the multicenter study, overall stroke rate was 4.2% (95% CI: 1.9–8.7). Systematic literature search identified two observational studies involving 576 patients that were eligible for meta-analysis. Amongst 741 pooled COVID-19 patients, overall stroke rate was 2.9% (95% CI: 1.9–4.5). Risk of acute stroke was increased for patients with severe compared to non-severe COVID-19 (RR = 4.18, 95% CI: 1.7–10.25; $P = 0.002$) with no evidence of heterogeneity ($I^2 = 0\%$, $P = 0.82$).

Conclusions: Synthesized analysis of data from our multicenter study and previously published cohorts indicates that severity of COVID-19 is associated with an increased risk of acute stroke.

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Introduction

Infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been linked to altered blood coagulability and increased risk of thromboembolic complications including venous and arterial embolism possibly mediated by systemic inflammatory injury of the endothelium, platelet activation and stasis [1,2]. Whilst high rates of pulmonary embolism and deep venous thrombosis have been reported in multiple coronavirus disease 2019 (COVID-19) cohorts, it remains poorly understood whether the disease might also manifest with acute stroke [3,4]. A retrospective observational study from Wuhan, China found cerebrovascular diseases during hospitalization in 5.7% of patients with severe COVID-19 and in 0.8% of patients with a non-severe course of the disease [5]. A possible pathophysiological link between COVID-19 and acute stroke has been further supported by individual case reports and small case series [6–8].

To explore a possible association between infection with SARS-CoV-2 and acute stroke we studied four cohorts of patients hospitalized for COVID-19 for occurrence of acute stroke, and pooled multicenter data with published data from the literature in a comprehensive meta-analysis.

Methods

Multicenter study

We included consecutive patients ≥18 years old with laboratory-confirmed diagnosis of COVID-19 who had been admitted to four participating hospitals with neurological departments including accredited stroke units (University Hospital Carl Gustav Carus Dresden, Klinikum Chemnitz gGmbH, Elblandklinikum Meissen, Städtisches Klinikum Dresden) in Saxony, Germany between 1 March 2020 and 30 April 2020 in our retrospective multicenter study. Locations of participating hospitals are illustrated in Fig. 1. Laboratory confirmation of SARS-CoV-2 was performed using real-time reverse transcription polymerase chain reaction (RT-PCR) assays (RealStar SARS-CoV-2 RT-PCR Kit RUO; Altona Diagnostics, Hamburg, Germany; Allplex 2019-nCoV Assay; Seegene, Seoul, Republic of Korea; GeneFinder COVID-19 Plus RealAmp; Osang Healtcare, Gyeonggi-do, Republic of Korea; BD SARS-CoV-2 Reagents for BD MAX System; BD Life Sciences, Sparks, NV, USA) from nasal or oropharyngeal swab.

This study was approved by the institutional review board (IRB) of Technical University Dresden (IRB number BO-EK-154042020). Due to the observational nature of the study design, informed consent was waived.

We obtained data on age, sex and vascular comorbidities including past history of cerebrovascular disease and venous thrombotic event, neurological symptoms during hospitalization not attributed to stroke and laboratory data relevant to inflammation and coagulation. Furthermore, we evaluated clinical course of COVID-19 using the classification by the National Health Commission guidelines on the Diagnosis and Treatment of COVID-19 [9]. Disease stages were categorized as ‘mild’ (mild symptoms absent

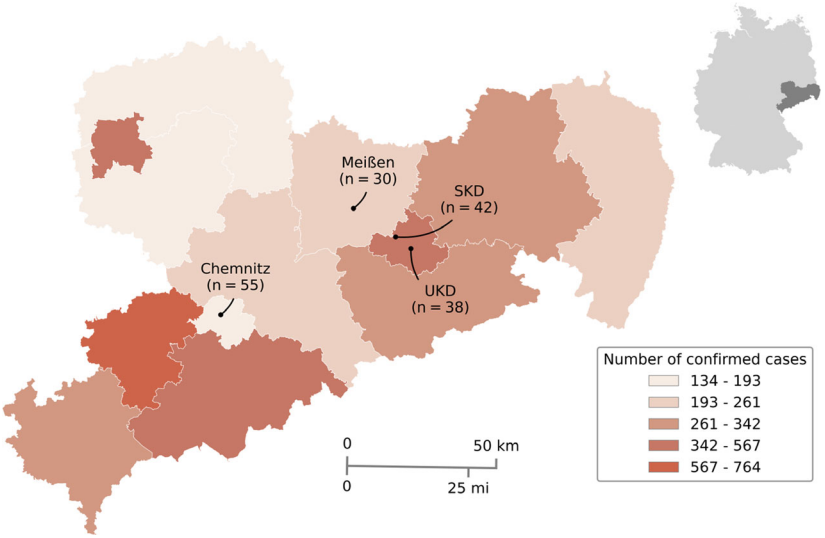

Figure 1 Location of participating sites in Saxony (color-coded map), Germany (grey map), with rates of confirmed infections with severe acute respiratory syndrome coronavirus 2 in Saxony based on epidemiological data provided by the Robert Koch Institute as of 30 April 2020 (www.rki.de/EN/Home/homepage_node.html). UKD, Universitätsklinikum Carl Gustav Carus Dresden (University Hospital Carl Gustav Carus Dresden); SKD, Städtisches Klinikum Dresden. [Colour figure can be viewed at wileyonlinelibrary.com]

signs of pneumonia on chest imaging), 'moderate' (fever, respiratory symptoms with radiologic evidence of pneumonia), 'severe' (respiratory distress with breathing frequency ≥30 per minute or resting oxygen saturation ≤93% or growth of pulmonary lesions >50% within 48 h or oxygenation index ≤300 mmHg), 'critical' (respiratory failure necessitating mechanical ventilation, hemodynamic shock, or any organ failure requiring intensive care). For data analysis, we dichotomized severity categories into 'severe' (subsuming disease stages 'severe' and 'critical') and 'non-severe' (subsuming 'mild' and 'moderate' stages). We additionally studied clinical course to categorize phase of COVID-19 according to Lean European Open Survey on SARS-CoV-2 Infected Patients (LEOSS) criteria distinguishing an 'uncomplicated' phase characterized by either absence of symptoms or occurrence of symptoms related to upper respiratory tract infection, nausea, emesis, diarrhea or fever from a 'complicated' phase defined by necessity of oxygen supplementation, decreased partial arterial oxygen pressure <70 mmHg or oxygen saturation <90% at room air, aspartate aminotransferase or alanine aminotransferase greater than fivefold upper limit normal, new cardiac arrhythmias, new pericardial effusion >1 cm, new heart failure with pulmonary edema, congestive hepatopathy or peripheral edema. Disease phase was classified 'critical' when use of catecholamines was necessary, life-threatening cardiac arrhythmia occurred, invasive or non-invasive mechanical ventilation was required, liver failure was present with international normalized ratio >1.55, kidney failure with necessity of dialysis occurred or organ failure was evident by a quick sepsis-related Sequential Organ Failure Assessment score ≥2. Lastly, patients were considered to have reached 'recovery' phase when they improved by one phase and showed defervescence [10]. To provide alternative categorical measures of COVID-19 severity, we obtained rates of in-hospital death versus survival and necessity of intensive care versus regular in-patient care until discharge. Furthermore, we defined 'any venous thrombotic event' including cerebral venous thrombosis, deep venous thrombosis and pulmonary embolism during hospitalization as additional severity outcome.

Acute stroke on admission or during hospitalization was defined as imaging-confirmed ischaemic stroke, transient ischaemic attack or intracerebral hemorrhage. Patients with COVID-19–related stroke were characterized for stroke localization, etiology according to trial of ORG 10172 in acute stroke treatment (TOAST) criteria [11] based on available results of cerebral, cardiac and vascular imaging [brain computed tomography (CT) or magnetic resonance imaging (MRI) scan, transthoracic echocardiography with additional transesophageal echocardiography in those with undetermined etiology/carotid and transcranial ultrasound, long-term electrocardiography]. Furthermore, they were characterized for vessel occlusion, acute treatment, elapsed time from admission to stroke onset as well as baseline National Institutes of Health Stroke Scale score.

Literature search and study eligibility

We performed a systematic review and meta-analysis in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations [12]. The protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42020187194).

Systematic literature search was undertaken using electronic databases MEDLINE accessed by PubMed, Embase and Cochrane Library for all available observational studies that reported on patients aged ≥18 years with acute stroke during hospitalization for laboratory-confirmed COVID-19. We also performed a snowball search in bibliographies of identified full-text articles and relevant review articles. We applied search terms 'COVID-19', 'stroke', 'cerebrovascular', 'cerebrovascular accident', 'cerebrovascular disease', 'cerebral infarction', 'cerebral ischaemia', 'intracerebral hemorrhage', 'transient ischaemic attack' as well as their combinations and associated Medical Subject Headings. Complete search strings as well as the PRISMA checklist are provided in Appendix S1. Systematic literature search covered articles from the earliest date available until our last search date 19 May 2020, with no language or other restrictions. Identified articles were eligible for meta-analysis when all of the following criteria were met: (i) randomized or non-randomized observational study reporting on a minimum of five patients aged ≥18 years who have been hospitalized for COVID-19 confirmed by molecular RT-PCR, (ii) data available on occurrence of acute stroke related to COVID-19 hospitalization and (iii) categorization of severity of COVID-19 according to study-specific definitions.

Two independent reviewers (T.S. and K.B.) assessed all identified articles by screening of titles, abstracts and full texts and resolved any disagreements by consensus. Full-text evaluation was performed where abstracts did not provide sufficient information for evaluation of methodology. We contacted corresponding authors of the identified articles if information was incomplete or any obscurities were present. Extraction of data from full text articles was undertaken by two independent reviewers (T.S. and K.B.).

All data were inserted into a standardized data extraction form (Excel; Microsoft, Redmond, WA, USA). We extracted information on first author, publication year, study design, sample size, demographic values, definition of COVID-19 severity and frequency of index stroke during hospitalization.

Rating of study quality

Study quality of articles included in the meta-analysis was evaluated using the Oxford Centre for Evidence-Based Medicine Rating Scale [13]. Two independent reviewers (T.S. and K.B.) performed quality assessment. Any disagreements were resolved by consensus.

Statistical analysis

Multicenter study

Continuous and non-continuous parameters are presented as median with interquartile range (IQR) for skewed data and percentages for proportional data. Univariate analyses were conducted using χ^2 test, Fisher exact test and Mann-Whitney U test, where applicable. Multivariable logistic regression was undertaken to determine the predictive value of severe COVID-19 for occurrence of acute stroke. The final multivariable model including *a priori* variables age, sex, arterial hypertension and diabetes mellitus was conducted using backward selection procedure with covariate removal if P value was ≥ 0.1.

Meta-analysis

Pooled rate of acute stroke was calculated with computation of 95% confidence intervals (95% CIs) using adjusted Wald method. We computed risk ratios (RRs) and their corresponding 95% CIs for severe COVID-19 from the absolute numbers of patients with and without acute stroke provided by each study. Studies with a zero cell were subject to continuity correction of 0.5 [14]. We excluded studies from respective analyses if two or more zero cell events were reported. Pooled RRs were computed using the DerSimonian and Laird random-effects model [15]. Meta-analysis was performed using a composite of COVID-19 severity subsuming any study-specific definition. Sensitivity analyses were carried out for cohorts using comparable definitions for disease severity. Missing outcome data were handled using a pairwise deletion method. We determined heterogeneity between studies using Cochran's Q test and I^2 statistics, with I^2 values of 0% to 40% indicating absent or low, 30% to 60% moderate, 50% to 90% substantial and 75% to 100% considerable heterogeneity [16]. Significance level of heterogeneity was set at $P < 0.1$.

Statistical significance was set at $P < 0.05$. All statistical analyses were conducted using the Stata software package (version 12.1; StataCorp, College Station, TX, USA).

Results

Multicenter study

Our multicenter cohort consisted of 165 patients (49.1% males, median age = 67 years, IQR 57–79), with RT-PCR–confirmed COVID-19 who were admitted to the four participating hospitals between 11 March 2020 and 30 April 2020. At the time of data acquisition, eight patients were still hospitalized. An overview of demographic values, comorbidities, laboratory data and outcomes is shown in Table 1. In total, seven patients experienced an acute ischaemic stroke ($n = 4$) or a transient ischaemic attack ($n = 3$), resulting in an overall rate of 4.2% (95% CI: 1.9–8.7). Intracerebral hemorrhage or cerebral venous thrombosis was not observed in the multicenter population. In five of these seven (71.4%) patients, index stroke was the primary reason for hospital admission, whereas two (28.6%) patients experienced an acute stroke following admission for COVID-19. Six of seven (85.7%) stroke patients developed a severe course of COVID-19, with necessity of intensive care in three of these cases. One (14.2%) stroke patient was admitted to the intensive care unit (ICU) for post-thrombectomy management rather than COVID-19–related complications. A detailed description of COVID-19 patients who experienced an acute stroke is provided in Table 2. Aside from a tendency toward a higher proportion of past history of cerebrovascular disease and increase in serum interleukin-6 level in stroke patients, no differences in demographics, vascular comorbidities and laboratory values were present compared to non-stroke patients (Table 1).

By multivariable backward selection analysis, only necessity of intensive care remained in the final model and emerged as independently associated with acute stroke (OR = 4.69, 95% CI: 1.0–21.9; $P = 0.05$), whereas none of the other pre-specified explanatory variables were predictive of acute stroke.

Systematic review

We retrieved a total of 759 abstracts from electronic databases and nine from bibliographies of published literature. After exclusion of duplicates and articles that did not fulfill eligibility criteria, two studies were included in the meta-analysis as described in detail in

Table 1 Characteristics of patients from multicenter cohort

	COVID-19, *n* = 165	+ Stroke, *n* = 7	− Stroke, *n* = 158	*P*
Demographic values				
Age, years, median (IQR)	67 (57–79)	72 (71–76)	67 (56–80)	0.3
Men, *n* (%)	81 (49.1)	3 (42.9)	78 (49.4)	1.0
Past vascular risk factors, *n* (%)				
Arterial hypertension	106 (64.2)	5 (71.4)	101 (63.9)	1.0
Hyperlipidemia	47 (28.5)	2 (28.6)	45 (28.5)	1.0
Diabetes mellitus	51 (30.9)	3 (42.9)	48 (30.4)	0.7
Atrial fibrillation	30 (18.2)	0 (0)	30 (19)	0.4
Tobacco use	22 (13.3)	2 (28.6)	20 (12.7)	0.2
Coronary heart disease	21 (12.7)	1 (14.3)	20 (12.7)	1.0
Cerebrovascular disease	24 (14.6)	3 (42.9)	21 (13.3)	0.06
Ischaemic stroke	19 (11.5)	3 (42.9)	16 (10.1)	
Transient ischaemic attack	2 (1.2)	0 (0)	2 (1.3)	
Intracerebral hemorrhage	3 (1.8)	0 (0)	3 (1.9)	
Venous thrombotic event	10 (6.1)	0 (0)	10 (6.3)	1.0
Cerebral venous thrombosis	0 (0)	0 (0)	0 (0)	
Pulmonary embolism	4 (2.4)	0 (0)	4 (2.5)	
Deep venous thrombosis	5 (3)	0 (0)	5 (3.2)	
Portal vein thrombosis	2 (1.2)	0 (0)	2 (1.3)	
Other neurological manifestations, *n* (%)				
Taste impairment	14 (8.5)	0 (0)	14 (8.9)	1.0
Smell impairment	9 (5.5)	0 (0)	9 (5.7)	1.0
Laboratory findings				
Lymphocyte count, admission, $\times 10^9$/l	0.9 (0.7–1.4)[a]	1.0 (0.8–1.5)	0.9 (0.7–1.3)[a]	0.6
Lymphocyte count, minimum, $\times 10^9$/l	0.9 (0.6–1.2)[a]	0.6 (0.4–0.8)	0.9 (0.6–1.2)[a]	0.09
Thrombocyte count, admission, $\times 10^9$/l	185 (148–254)	197 (164–216)	180 (148–256)	0.9
Thrombocyte count, minimum, $\times 10^9$/l	161 (120–226)	172 (105–197)	160 (121–229)	0.7
D-dimer, admission, mg/l	0.9 (0.5–1.8)	0.8 (0.6–1.5)	0.9 (0.5–1.9)	0.8
D-dimer, maximum, mg/l	1.2 (0.5–3.4)	1.2 (0.6–3.3)	1.2 (0.5–3.4)	0.9
INR, admission	1 (1–1.2)	1 (1–1.1)	1 (1–1.2)	0.6
INR, maximum	1.1 (1–1.4)	1.1 (1.1–1.3)	1.1 (1–1.4)	0.6
C-reactive protein, admission, mg/l	41.5 (10.7–91.5)	50.2 (4.7–92.5)	41.4 (11.1–91.5)	0.8
C-reactive protein, maximum, mg/l	85.1 (34.9–174.8)	157.6 (55.4–191.8)	82.3 (33.1–174.8)	0.3
Interleukin-6 admission, ng/l	30.8 (7.7–74.3)[a]	46.3 (9.6–53.1)	29.1 (7.7–74.3)[a]	0.9
Interleukin-6 maximum, ng/l	35.4 (7.3–89.2)[a]	46.3 (14.1–119)	34 (7.3–85.1)[a]	0.7
Severity outcomes, *n* (%)				
Disease severity by NHC				0.8
Mild/moderate	46 (27.9)	1 (14.3)	45 (28.5)	
Severe	77 (46.7)	4 (57.1)	73 (46.2)	
Critical	42 (25.5)	2 (28.6)	40 (25.3)	
Stages of disease by LEOSS				0.7
Uncomplicated	43 (26)	1 (14.3)	42 (26.6)	
Complicated	77 (46.7)	3 (42.9)	74 (46.8)	
Critical	45 (27.3)	3 (42.9)	42 (26.6)	
Recovery	101/164 (61.6)[b]	4 (57.1)	97 (61.8)	1.0
Intensive care treatment	39 (23.6)	4 (57.1)	35 (22.2)	0.06
Any venous thrombotic event	18 (10.9)	1 (14.3)	17 (10.8)	0.6
Cerebral venous thrombosis	0 (0)	0 (0)	0 (0)	
Pulmonary embolism	15 (9.1)	1 (14.3)	14 (8.9)	
Deep venous thrombosis	11 (6.7)	1 (14.3)	10 (6.3)	
In-hospital death	32/157 (20.4)[b]	2 (20.4)	30 (20)	0.6

INR, international normalized ratio; IQR, interquartile range; LEOSS, Lean European Open Survey on SARS CoV II Infected Patients; NHC, National Health Commission. [a]Parameters with data available in <70% of the study population. [b]According to available data and patients discharged at the time of analysis.

Table 3 [17,18]. The flowchart showing the systematic screening and selection process is depicted in Fig. 2. The included studies consisted of multicentric cohorts from Italy and China, respectively, and were of descriptive observational design. Severity of COVID-19 in these studies was defined either clinically according to American Thoracic Society guidelines for community-acquired pneumonia or by necessity of ICU

Table 2 Clinical characteristics and outcomes related to stroke in the COVID-19 patient population

Patient	Age, years	Sex	Stroke type	Stroke territory	Stroke etiology	Vessel occlusion	Acute therapy	Admission to stroke onset, days	NIHSS at stroke onset	COVID-19 severity	Survival
1	65	M	AIS	Anterior circulation	Undetermined	None	None	24	32	Severe/ICU	No
2	72	F	AIS	Posterior circulation	Undetermined	None	None	0	—	Severe/ general ward	Yes
3	71	F	TIA	Anterior circulation	Undetermined	None	None	0	3	Severe/ general ward	Yes
4	73	F	TIA	Anterior circulation	Undetermined	None	None	0	2	Severe/ICU	Yes
5	76	M	TIA	Posterior circulation	Undetermined	None	None	0	—	Severe/ICU	Yes
6	83	M	AIS	Anterior circulation	Cardioembolism[a]	Distal MCA	None	1	17	Severe/ general ward	No
7	71	F	AIS	Anterior circulation	Cardioembolism[a]	Distal MCA	IVT/ EVT	0	6	Non-severe/ ICU	Yes

AIS, acute ischaemic stroke; EVT, endovascular therapy; F, female; ICU, intensive care unit; IVT, intravenous thrombolysis; M, male; MCA, middle cerebral artery; NIHSS, National Institutes of Health Stroke Scale; TIA, transient ischaemic attack. [a]Diagnosis based on evidence of atrial fibrillation.

Table 3 Characteristics of the descriptive observational studies included in the quantitative data synthesis

Study	Study design/ quality[a]	Severity outcomes	Study size, *n*	Age, years	Male, %	Acute stroke, *n* %	Observational period
Lodigiani *et al*., 2020	Descriptive/4	ICU vs. general ward	48 vs. 314	61 (14) vs. 68 (22)[b]	80.3 vs. 65.7	3 (6.3) vs. 6 (1.9)	Since February 2020
Mao *et al*., 2020	Descriptive/4	Severe vs. non-severe[c]	88 vs. 126	58.2 (15) vs. 48.9 (14.7)[d]	50 vs. 34.1	5 (5.7) vs.1 (0.8)	16 January 2020–19 February 2020

ICU, intensive care unit. [a]According to quality rating scheme by the Oxford Centre for Evidence-Based Medicine. [b]Median (interquartile range). [c]According to definitions by American Thoracic Society guidelines for community-acquired pneumonia. [d]Mean ± standard deviation

treatment [17,18]. Of 576 laboratory-confirmed COVID-19 patients (60.9% males, average ages ranging from 53 to 66 years) reported in these studies, 15 patients (2.6%) were reported of having a stroke related to COVID-19 hospitalization (acute ischaemic stroke, $n = 14$; intracerebral hemorrhage, $n = 1$).

Meta-analysis

Meta-analysis including individual patient data from our multicenter cohort consisted of 741 laboratory-confirmed COVID-19 patients (58.3% males, average age ranging from 52 to 67 years). The overall rate of stroke was 2.9% (95% CI: 1.9–4.5) in the pooled COVID-19 population. When dichotomizing by disease severity, the overall rate of stroke was 5.5% (95% CI: 3.2–9.1) in patients with severe COVID-19 and 1.7% (95% CI: 0.8–3.3) in those with non-severe manifestation of the disease.

On quantitative data synthesis, severe COVID-19 was associated with an increased risk of acute stroke (RR = 4.18, 95% CI: 1.7–10.25; $P = 0.002$; Fig. 3) with no evidence of heterogeneity across included studies ($I^2 = 0\%$, $P = 0.82$). This association remained unchanged when we solely pooled our multicenter data with the published Italian cohort that defined disease severity by necessity of intensive care (RR = 3.72, 95% CI: 1.38–10.0; $P = 0.009$). When multicenter data were pooled with only the Chinese cohort defining severity by clinical parameters, we still observed a tendency toward an increased risk of acute stroke for severe COVID-19 (RR = 3.97, 95% CI: 0.89–17.63; $P = 0.07$). There was no between-study heterogeneity identified in these sensitivity analyses ($I^2 = 0\%$, $P = 0.79$ and $I^2 = 0\%$, $P = 0.45$, respectively).

Study quality

Studies included in the meta-analysis were consistently graded as level of evidence 4 according to Oxford Centre for Evidence-Based Medicine rating scale quality (Table 3). Publication bias was not assessed due to the low number of included studies.

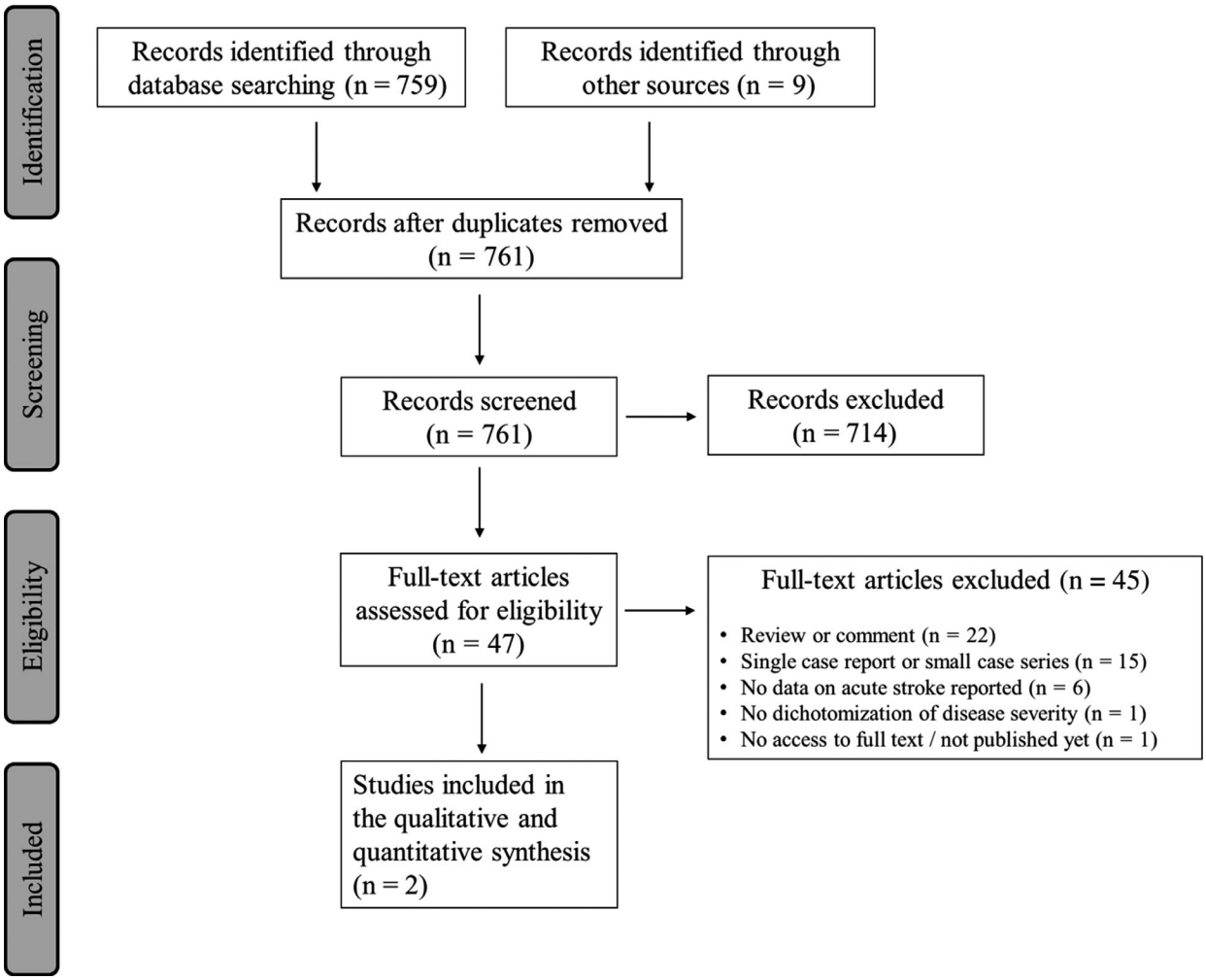

Figure 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart illustrating systematic screening and selection process of published studies.

Discussion

The results of this study pooling observational multicenter data from Germany with published data from cohorts in Italy and China suggest that patients with severe course of COVID-19 are at increased risk of acute ischaemic stroke.

Our investigation has several strengths. We pooled data of a well-characterized regional multicenter cohort with published data from geographically distant cohorts, substantiating generalizability of our observations. It is noteworthy that each of the regions providing data ranks amongst the 10 countries most affected by the pandemic [19]. External validity is further supported by consistency of observed severity-dependent stroke rates amongst cohorts and absence of statistical heterogeneity across studies included in the quantitative synthesis. All hospitals participating in our multicenter study had accredited stroke units with 24/7 stroke service available, allowing guideline-based hyperacute evaluation and treatment of cerebrovascular diseases. Furthermore, with the exception of two cases, all patients included in our multicenter analysis had a cerebral ischaemic event, consistent with the possibility of an underlying COVID-19–related coagulopathy. There are limitations to our study. Due to the low number of eligible studies identified from the literature and absence of statistical heterogeneity, a meta-regression analysis to elucidate to what extent the risk association between COVID-19 severity and acute stroke was independent of covariates was not considered expedient. Consistently, assessment of publication bias was not undertaken in consideration of the limited number of published studies included in the quantitative synthesis [20]. Furthermore, we cannot rule out differences in definition of transient

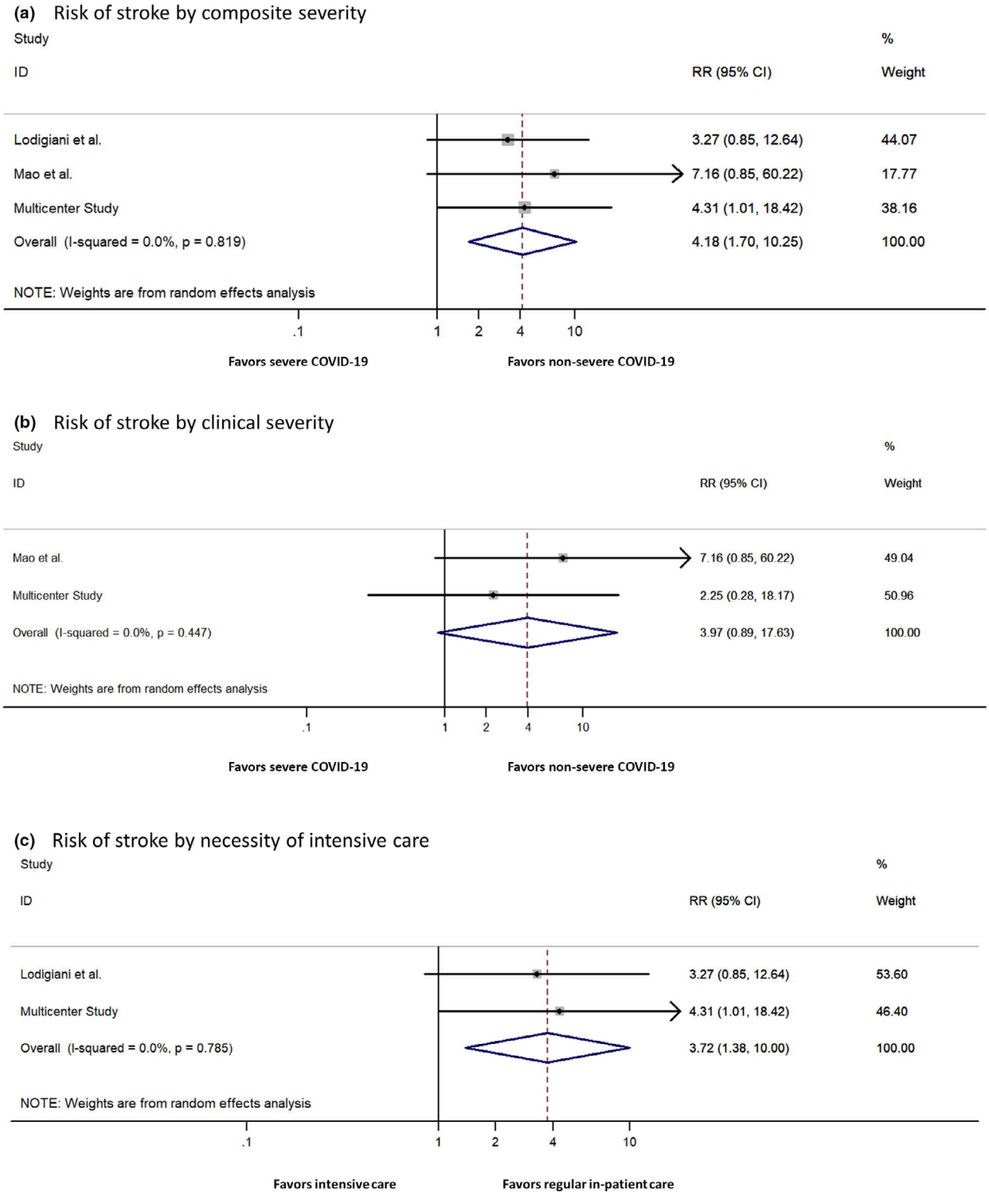

Figure 3 Forest plots of stroke risk associated with severe clinical manifestation of COVID-19 for composite severity subsuming all definitions of severity as reported by included studies (a), as well as for clusters of studies defining severity by grading of clinical parameters (b) and whether patients required intensive care (c). Individual patient data from German multicenter cohort was evaluated for severity based on the Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment [9]. CI, confidence interval; RR, risk ratio. [Colour figure can be viewed at wileyonlinelibrary.com]

ischaemic attack amongst included studies. We cannot rule out that a proportion of asymptomatic COVID-19 in-patients might have remained undetected since participating hospitals have individually adapted their testing strategies to the evolving situation after the outbreak. Lastly, the risk of acute stroke might have been underestimated in our study in severely ill patients who required mechanical ventilation, impeding detection of clinical neurological symptoms. We cannot comment on whether the increased risk of stroke observed in severe COVID-19 patients is eventually different from that in patients with critical illness resulting from other viral pathogens, as data on coincident in-hospital strokes in the general population are largely lacking.

The exact mechanism whereby COVID-19 may increase risk of acute stroke is unclear. Previous research suggested that COVID-19 leads to a hypercoagulable state mediated by elevation of prothrombotic factors, stasis related to immobilization and endothelial injury either by direct virus invasion of endothelial cells by mediators of acute systemic inflammation such as interleukin-6 [21,22]. Interestingly, only one of the seven stroke patients included in our multicenter study experienced deep venous thrombosis and pulmonary embolism during hospitalization, possibly consistent with a rather primary arterial manifestation of COVID-19–related coagulopathy in our study population. Moreover, in five (71.4%) of the seven patients, detailed cardiovascular assessment has not identified etiology of stroke constituting a far higher proportion than observed in stroke populations not infected with SARS-CoV-2, where diagnosis of stroke of undetermined etiology following TOAST criteria accounts for approximately one-third of all strokes [23,24]. An equally high rate of cryptogenic stroke has been found in a recently published COVID-19 cohort comprising 32 stroke patients from the New York metropolitan area, of whom 21 (65.6%) had undetermined etiology [25]. The low yield of standard workup for stroke etiology might support the hypothesis of a COVID-19–specific mechanism mediating acute stroke in these patients and raises an urgent need for further prospective investigation including in-depth analysis of stroke pattern and assessment of the possibility of asymptomatic deep venous thrombosis with paradox embolism. Furthermore, five out of seven patients in our multicenter cohort presented to the emergency room with acute stroke prior to developing any respiratory symptoms, raising the possibility of primary cerebrovascular manifestation of COVID-19. Consistently, acute stroke was the reason for admission in almost half of the SARS-CoV-2–positive stroke patients from New York [25]. Our pooled analysis comprising regional multicenter data from the literature showed that a past history of cerebrovascular disease might be linked to an increased stroke risk in COVID-19 patients. This underscores the necessity of exploring the role of cerebrovascular pathology related to SARS-CoV-2 infection on a pathophysiological level. It is noteworthy that we do not know what proportion of stroke patients without any symptoms commonly attributed to COVID-19 might have been left undetected in our multicenter study. We recently showed in an observational 4-week single-center study of universal testing for SARS-CoV-2 that none of the included 116 consecutive code stroke patients tested positive [26]. However, a very low yield of universal testing for SARS-CoV-2 in stroke patients requires confirmation in larger study populations.

None of the stroke patients from our multicenter COVID-19 cohort had neurological symptoms previously linked to infection with SARS-CoV-2 such as impairment of taste or smell. In a cohort from the Wuhan region in China, impaired taste or smell was noted in 7.1% and 6.3% of patients with non-severe COVID-19, respectively, but only in 3.4% of those severely affected by the disease [5]. A large prospective cohort from Italy found taste or smell dysfunction in 64% of mildly symptomatic patients who tested positive for SARS-CoV-2 [27]. Taken together, these observations indicate that cerebrovascular manifestations might be a consequence of disease-mediated hypercoagulability rather than of direct cerebral neuroinvasion of SARS-CoV-2 as a recently considered possible cause of disease-related olfactory dysfunction [28]. Also, the observation that olfactory dysfunction frequently occurs in mildly affected patients supports the hypothesis that non-vascular neurological manifestations follow different pathophysiological mechanisms and are less dependent of disease severity than cerebrovascular manifestations.

Conclusion

Our pooled data from a German multicenter cohort of COVID-19 patients and published data from the literature suggests that patients with a severe course of COVID-19 have an increased risk of acute stroke, underscoring the necessity of clinical neurological monitoring in patients infected with SARS-CoV-2 and warranting further investigation of the underlying pathophysiology.

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Disclosure of conflicts of interest

The authors declare no financial or other conflicts of interest.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PRISMA 2009 checklist.

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